Coagulopathy in trauma patients: what are the main influence factors?

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Purpose of review

Coagulopathy and bleeding after severe injury is a common problem. Whenever caring for critically ill patients, clinicians must anticipate, recognize and manage the coagulopathy of trauma. When left untreated, cardiovascular shock and multiorgan system failure ensue. Uncompensated hemorrhage often culminates in death, highlighting the significance of recognizing the main influences in coagulopathy of trauma.

Recent findings

With recent improvements in prehospital care, trauma specialists face more challenging cases than ever before. Hemostatic transfusion strategies, with early and more aggressive use of plasma, platelets, cryoprecipitate and coagulation factor isolates, decrease blood loss in trauma patients. Combined with point-of-care testing for thromboelastography, coagulation panels, lactate and local pO_2, there is an opportunity for frontline trauma clinicians to directly improve patient outcomes.

Summary

Although mortality previously was thought to be summarily independent of medical interventions and resuscitations, we now know the opposite to be true; it is our expectation and indeed our obligation to recognize and manage the coagulopathy of trauma better than in past years. In as much as we continue to prevent acidosis, hypothermia and the progressive coagulopathy following injury, trauma victims the world over are benefiting and surviving longer, living proof that demonstrates the utility of managing the coagulopathy of trauma.

Keywords

coagulopathy, management, resuscitation, trauma

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Introduction

With recent improvements in prehospital care, trauma specialists are facing more challenging cases than ever before – patients who would not have made it to the hospital in past years. With the advent of rapid point-of-care testing for thromboelastography (TEG), coagulation panels, lactate and local pO_2, there is an opportunity for frontline trauma clinicians to directly improve patient outcomes. Although once it was thought that mortality was summarily independent of medical interventions and resuscitations, we now know the opposite to be true; it is our expectation and indeed our obligation to recognize and manage the coagulopathy of trauma better than in past years. In as much as we continue to prevent acidosis, hypothermia and the progressive coagulopathy following injury, trauma victims the world over are benefiting and surviving longer. Quite literally, they are the living proof that demonstrates the utility of managing the coagulopathy of trauma.

Historical perspective

Major advancements in medical transport times and the use of new tourniquets to prevent exsanguination from extremity injuries allow today's trauma victims to reach medical treatment facilities for definitive treatment sooner and in better condition than was previously possible. It is no surprise then that potentially preventable morbidity and mortality stem from inadequate control of hemorrhage and coagulopathic development from the time of injury to the time of treatment within a medical facility. In fact, when investigating uncontrollable bleeding in US soldiers engaged in combat, military researchers concluded that uncontrolled bleeding accounts for over one-third of trauma-related deaths and is the leading cause of potentially preventable deaths following major trauma [1,2,3•]. The study [2] details the incidence, causative mechanisms and effects of traumatic hemorrhage, both domestic and international.

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Hemorrhage ranks second in overall causes of prehospital deaths according to Tieu *et al.* [4••]. Massive hemorrhage in major trauma victims correlates to high mortality in the early postoperative period [5]. Whether it is a combat medic on the battlefield, a civilian paramedic in the prehospital environment or a trauma physician in a tertiary care center, understanding the principles of early resuscitative treatment and hemorrhage stabilization will lead to improved patient outcomes and decreased coagulopathic complications.

Perioperative and emergency medicine literature describe the concept of trauma damage control for reducing hemorrhage and prevention of hemorrhagic shock to improve morbidity and mortality outcomes [3•,6••,7•]. Traditional practices focus on healthcare providers and first responders treating hypotension, acidosis and hypothermia with warm crystalloid and then concentrating secondary efforts on preventing coagulopathy and achieving surgical control of bleeding. Although previously calling for immediate and aggressive intravenous fluid resuscitation of patients in hemorrhagic shock, current guidelines in *Advanced Trauma Life Support* have been revised to direct care toward managing controllable hemorrhage and leaning toward a more hemostatic goal for the resuscitation rather than just prevention of hypotension and circulatory collapse [8,9]. The study [9] demonstrated yet another reason to aggressively pursue normothermia. Temperature alterations disrupt the coagulation cascade by inhibition of the effects of von Willebrand factor (vWF).

The conventional approach of immediate volume resuscitation with 2 l isotonic crystalloids and plasma-poor red blood cells (RBCs) to manage early active hemorrhage is often counterproductive and may potentiate what is commonly referred to as the 'lethal triad of death': hypothermia, acidosis and progressive coagulopathy. Even though these resuscitative fluids may promote oxygen delivery and tissue perfusion, RBCs, crystalloid and colloid solutions often carry a heavy price tag in and of themselves. They disrupt electrolyte balance, further dilute coagulation factors and impair clot formation. This can result in greater transfusion requirements owing to periods of raised blood pressure, the so-called 'pop the clot' phenomenon seen during fluid bolus administration [9]. In fact, with the development of this lethal triad, Cosgriff *et al.* [10] have shown that the sum and severity of these components along with injury severity can account for the incidence of coagulopathy approaching 100% and mortality reaching almost 60%. A new concept of 'damage control resuscitation' has emerged that addresses the entire triad of death on admission to medical treatment facilities and calls into question how soon coagulation factor replacement should be used in early active hemorrhage following trauma [11••,12••,13••].

Objectives

Following combat-related injury or civilian trauma, the anesthesiologist, surgeon, intensivist and emergency medicine physician must all work in conjunction as a team to control bleeding and prevent exsanguination. Although this starts preoperatively, it must continue during the intraoperative and postoperative periods. Optimal management of life-threatening uncontrollable bleeding, whether due to vascular injury or gross coagulopathy, requires a multidisciplinary approach to include surgical interventions (i.e. suture ligation and electrocautery) and resuscitative efforts focused on directing blood component therapy to optimally achieve hemostasis [7•].

Understanding the main factors that influence coagulopathy in trauma patients is key to improved outcomes such as increased survival and decreased morbidity following trauma. These coagulopathic concerns start immediately after the trauma and continue throughout the perioperative course [3•,14••]. In this review, we will discuss the factors that influence the coagulopathy of trauma and how each component affects patient outcomes and clinical decision-making. In addition, we will briefly address treatment and management strategies to proactively limit the complications and sequelae often associated with the lethal triad of death.

Factors affecting the coagulopathy in trauma patients

The body's intrinsic hemostatic regulatory mechanisms involve a principal balance between clot formation and breakdown. Following endothelial injury, clot initiation occurs through vasoconstriction, platelet plug creation, fibrin mesh formation and lysis [2]. Factors that influence the coagulopathy of trauma can also be divided into four main groups: hypothermia, acidosis, complications of resuscitation and additional factors.

Hypothermia

Hypothermia, defined as core body temperature of less than 35°C, is a key factor in the coagulopathy after trauma and uncontrolled bleeding in the operating room [2,6••,14••,15•,16•,17••,18]. Martini *et al.* [18] studied the isolated effects of these procoagulopathic conditions *in situ* using a porcine model. The American Society of Anesthesiology (ASA) recognized the importance of monitoring temperature for management of hypothermia when it issued the ASA standard for temperature monitoring. This is the recommendation that 'every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected' [19]. The study [19] was amongst the first to stress the importance and need for intraoperative temperature

monitoring and management. Hypothermia either following trauma or present intraoperatively is secondary to one of the four mechanisms of heat loss. These include conduction, convection, radiation and evaporation. Addressing these mechanisms may assist in the maintenance of normothermia and prevention of the development of hypothermia, which is all too often detrimental in the case of the bleeding trauma patient. A recent study by Dirkmann *et al.* [6••] demonstrated impaired stability of clots as well as slowed initiation and propagation of coagulation during periods of hypothermia. Specifically, hypothermia affects platelet activation and adhesion at the molecular level by inhibiting the interaction of vWF and platelet glycoprotein Ib–IX–V complex [9]. When patients lack adequate compensatory thermoregulatory mechanisms required to maintain normothermia in response to cold stressors, avoidance of hypothermia to prevent coagulopathy is an important practice strategy [14••,15•,17••].

In addition to the heat loss associated with trauma and the prehospital phase, intraoperative heat loss during initiation and maintenance of general anesthesia results initially in a rapid decrease in core temperature followed by a linear reduction in core temperature; this is discussed in a chapter taken from *Miller's Anesthesia* textbook [20], the most commonly accepted 'bible' of anesthesia texts. This characteristic anesthesia-induced pattern of hypothermia is compounded by rapid intravascular volume expansion with relatively cold intravenous fluids or blood components during rapid administration of resuscitative products in the face of continued operative or traumatic hemorrhage. The hypothermic insult is associated with a decrease in thrombin generation as well as compromised formation of both platelet plugs and fibrin clots [9,18]. In addition to the qualitative platelet deficit, there is also an increase in lysis of clots.

Acidosis

Usually characterized by an acidemic pH of less than 7.35, acidosis also has profound effects on coagulopathy following trauma and large fluid resuscitations with supraphysiologic concentrations of chloride relative to sodium [21••,22•]. A common strategy for treating acute hypotension in the operating room or during first response in field medicine is the bolus administration of crystalloid solutions. Although isotonic saline is often chosen, balanced crystalloid solutions such as Ringer's lactate solution are also common. Even after assuming an intact Cori cycle and the absence of shock liver, lactate can impose an acid load that is poorly tolerated by physiologic buffer systems that are already compromised [23]. This has led some researchers to examine buffers as mediators to improve the coagulopathy of trauma, although results have not been inspiring [24••].

Recent studies have demonstrated that although acidosis alone can worsen coagulopathy by inhibiting the enzyme complexes that are vital to clot formation, the combination of acidosis and hypothermia can lead to severe coagulopathy and disastrous consequences. Dirkmann *et al.* [6••] showed a synergistic effect on impairment of coagulation when acidosis was added to existing hypothermia but failed to show a significant change in all viscoelastic properties of clot formation (except clot lysis) when studying acidosis alone. In addition, the severity of acidosis and hypothermia in this study showed more impairment in coagulation parameters than the mathematical sum of each. Martini *et al.* [18] showed increased bleeding time and thrombin generation when severe acidosis and hypothermia were combined in a swine model.

Complications of resuscitation and transfusion therapy

The perfusion insult and acidosis seen after trauma is worsened by the commonly used blood preservative citrate phosphate dextrose (with adenine or adenine, dextrose, sorbitol, sodium chloride and mannitol) and by old blood [25••,26••]. Citrate phosphate dextrose and citrate phosphate dextrose adenine solutions are often responsible for low levels of 2,3-diphosphoglyceric acid. The longer the blood is banked (especially after 21 days), the greater the acidosis seen in conjunction with CO_2 accumulation and buildup of acids as byproducts of RBC metabolism [13••,25••]. The resulting left shift in the hemoglobin (Hb)–O_2-carrying curve means decreased oxygen release from Hb. A dilutional coagulopathy, seen during initial and ongoing resuscitations with fluids such as crystalloids and packed RBCs, which are poor in clotting factors, is the unwanted byproduct of focusing on restoration of intravascular volume rather than hemostasis [12••,27]. In doing so, well meaning but ill-informed clinicians provide fodder for the adage 'drive the pressure and pop the clot'. Once translated, the study [27] offers a compelling argument for deliberate hypotensive resuscitation of a bleeding trauma patient. As discussed previously, hypothermia can, in and of itself, cause tremendous dysfunction within the coagulation cascade. Cold storage requirements for erythrocytes, plasma and cryoprecipitate compound the sting of trauma coagulopathy by leading to qualitative platelet defects and impaired coagulation enzyme pathways when normothermia is compromised after transfusion. When these functional defects are considered along with the acidic milieu of a typical 21-day-old unit of RBCs with pH often approximating 6.3, it is clear that RBC transfusion is no magic bullet [25••,28•].

Additional factors

In addition to acidosis, hypothermia and hemodilution, several additional factors are implicated in the coagulopathy of trauma. Although often unmentioned,

hemorrhage and extravasation of clotting factors is as detrimental as the consumption of platelets and coagulation factors, often referred to as consumption coagulopathy [7•]. Increased fibrinolysis is associated with hypothermia, anoxia, perfusion deficits and tissue damage [10,29]. The overall pattern of fibrinolysis in the trauma population is particularly puzzling as both hyperfibrinolytic and hypofibrinolytic states have been encountered [30••]. Point-of-care TEG and coagulation function tests demonstrate their merits in these circumstances, whereas laboratory-based routine coagulation panels understate the coagulopathy as they are assayed at 37°C and often require 30–60 min to provide a result.

Several other causes have also been identified in the altered coagulatory profile of trauma patients. Detrimental effects of colloids such as hetastarches, in doses of more than 15–20 ml/kg, are believed to impair the coagulatory profile as well [2]. Both hemodilution and platelet impairment are implicated when these resuscitative fluids are chosen to replete intravascular volume. Because ionized calcium is required for normal clotting, hypocalcemia often leads to deficits in the clotting cascade [31•]. The clinical course following severe trauma often resembles disseminated intravascular coagulation, with similar findings such as multiple intravascular clots and discrete necrotic lesions [32].

Monitoring

Traditionally, when blood products and fluids are administered during ongoing surgical bleeding, physicians have had to rely on monitoring frequent serial laboratory test results such as prothrombin time, activated partial thromboplastin time, platelet count, blood fibrinogen levels and fibrin degradation products [29,33•]. These results may be used to guide transfusion requirements and improve coagulation profiles [34•]. Clinically, however, this is not the case because from the time coagulation samples are sent for laboratory analysis to the time results are available, 30–60 min may routinely pass. This is enough time for the clinical picture to completely change and deteriorate for victims of severe trauma. Although the duration of obtaining laboratory results is standard, the utility of these relatively delayed results for clinical decision-making is limited because of the constant change in coagulation profile during ongoing resuscitative efforts. Point-of-care TEG and coagulation function tests demonstrate their merits in these circumstances, whereas laboratory-based routine coagulation panels are neither time-sensitive nor do they accurately reflect the coagulopathy coincident with hypothermia as they are assayed at 37°C [35••].

Clinically relevant laboratory information that may affect a physician's decision to treat a specific form of coagulopathy in the trauma patient requires rapid acquisition and quantification of the coagulation process as a whole. TEG provides a dynamic and graphic qualitative depiction of the coagulation capacity based on viscoelastic properties of blood, and it also provides quantitative information based on clot initiation and maturation. TEG determines the time for initial fibrin formation, the rate of fibrin deposition, clot consistency, the rate of clot formation and lysis [34•]. However, operation and analysis of TEG data often require clinicians and laboratory personnel with experience in interpreting TEG graphs. Familiarity and experience with clinical TEGs can be very beneficial when it comes to guiding the choice of resuscitative fluids and directing blood component therapy [36••,37•].

Treatments

Although recognition of the factors implicated in the coagulopathy of trauma is important, the prevention and management of this coagulopathy is paramount to improving outcomes. Options include using an increased ratio of plasma to erythrocytes, increased use of cryoprecipitate and platelets, recombinant factor VIIa (rFVIIa) and coagulation adjuncts such as human fibrinogen extracts, desmopressin acetate (DDAVP) and conjugated estrogens [14••,21••]. Rather than clinging to a staid practice that compounds the coagulation defect, early aggressive use of plasma, platelets and cryoprecipitate combined with component-directed transfusion therapy driven by TEG will improve short-term considerations such as cumulative transfusion requirements as well as long-term outcomes such as survival [11••,38••]. Although the debate continues over the need and the likelihood of large multicenter prospective randomized clinical trials investigating the role of rFVIIa, fresh whole blood and lyophilized blood products such as plasma and platelets in the management of marked coagulopathy, clinicians will need to rely on their own clinical judgments and relevant studies available to guide their damage control resuscitation and correction of trauma coagulopathy [13••,39••,40].

In addition, use of tourniquets and topical hemostatic agents help stem active hemorrhage and reduce the need for further dilution of clotting factors with fluids other than fresh whole blood [1,3•,13••,41]. This goes hand in hand with deliberate limitation of hetastarch and colloids associated with aggravated hemodilution and impaired coagulatory profiles [1,2]. In decreasing actual blood loss, native clotting factors will remain *in situ*, whereas hemostatic ground is gained most easily [29,42].

Normothermic maintenance is stressed and mandates the use of fluid warmers, heated trauma operative suites and temperature conservation technologies to include intravascular temperature management catheters and surface warming applications [17••,21••]. The prevention

and treatment of acidosis must be stressed throughout the hospital course, and perfusion deficits must be limited to minimize lactic acidosis [7•]. Along with frequent monitoring of acid–base status, clinicians must stay vigilant to ward off the acute hypocalcemia so common after transfusion with citrate-rich blood products [4••]. A key player in the coagulation cascade as factor IV, ionized calcium should be monitored throughout the resuscitation to avoid the pitfalls of hypocalcemia, which, through vigilant monitoring, is readily corrected. Acute hypocalcemia of trauma is most often secondary to either citrate toxicity or hypothermia [43].

Conclusion

Although the coagulation defects following severe trauma may not be completely reversible, the dividends are great for any improvement toward hemostasis. Hemorrhage-control strategies such as extremity tourniquet use, deliberate hypotension and damage control resuscitation must be used in conjunction with rFVIIa, DDAVP, conjugated estrogens and lyophilized blood products. Revised transfusion ratios call for early and more aggressive use of plasma and fibrinogen-rich blood products, including fresh whole blood for emergency use in severe hemorrhage and massive transfusion. The coagulopathy of trauma is laden with opportunities for clinicians to intervene on behalf of the patient and address the factors responsible for the deficit: acidosis, hypothermia, progressive coagulopathy, hypocalcemia, consumption and hyperfibrinolysis. Aggressive monitoring and fundamental avoidance of these factors are critical in improving patient outcomes in trauma.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 321–322).

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